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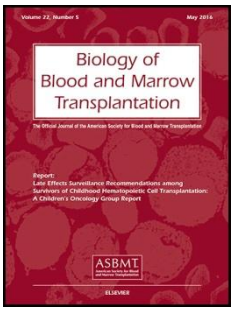

Title: Allogeneic hematopoietic cell transplantation following the use of hypomethylating agents among patients with relapsed or refractory AML: Findings from an international retrospective study

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Allogeneic hematopoietic cell transplantation following the use of hypomethylating agents among patients with relapsed or refractory AML: Findings from an international retrospective study

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Running title: Transplant outcomes after HMA therapy for RR-AML
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Highlights:

- In this large retrospective multicenter international cohort study including 655 primary treatment refractory or relapsed (RR)-AML treated with hypomethylating agents (HMAs), only a small subset of patients (5.6%) underwent HSCT after stop of HMA therapy.
- Only a minority of patients treated with HMA and subsequent HSCT (6 patients in the entire cohort, <1%) were long-term survivors.

To the Editor

Patients with primary refractory and relapsed (RR)-AML, particularly older adults, have dismal outcomes and limited therapeutic options are available[1]. Allogeneic hematopoietic cell transplant (HSCT) is the only potentially curative treatment in this setting[2, 3]. However, achieving disease control is generally necessary for successful HSCT outcomes. Intensive chemotherapy is the commonly used modality to achieve CR for patients with RR-AML; however, CR rates are generally do not exceed 20-40% and intensive therapy is associated with increased risks of mortality and morbidity as well as prolonged hospitalization. Given their tolerability, hypomethylating agents (HMAs) have been used in patients with AML, usually in frontline setting, who are unfit for intensive chemotherapy[1]. In a prior multicenter study, we have shown that HMAs result in CR/CR with incomplete count recovery (CRi) in 16% of patients with RR-AML while offering the opportunity of outpatient therapy and lower risk of therapy-related complications[4]. Most of the data regarding transplant outcomes among patients with RR-AML comes from trials and analyses of patients who received intensive salvage chemotherapy[5]. Several intensive chemotherapy regimens have been studied, however, there is no clear evidence of superiority of any particular regimen[5]. In contrast, little is known about the transplant outcomes for those patients with RR AML who are treated with HMA as salvage therapy prior to transplant.

Using a large multicenter international database, we analyzed characteristics and clinical outcomes of the subgroup of RR-AML patients who underwent HSCT after HMA salvage therapy. Data of patients treated with HMAs for RR-AML were collected for a period spanning 2006 to 2016, from 7 centers in the United States and 4 centers in Europe. For the subgroup of

patients who underwent HSCT after HMA therapy, we assessed type of graft and conditioning regimen, lines of therapy post HMA and prior to HSCT, a well as any post HSCT therapies. Furthermore, we analyzed the rate and severity of acute and chronic graft-versus-host-disease (GVHD) as well as 30-day and long-term mortality post-transplant and their respective predictors. Kaplan-Meier methods were used to estimate overall survival (OS) from the start of HMA therapy to death or end of follow-up.

Of 655 patients in the database, 16% achieved a CR/CRi with HMA therapy, and only 37 patients (5.6% of the entire cohort) underwent HSCT at one point after receiving HMA salvage therapy (**Table 1**). Of these patients, 16 (43.2%) had relapsed and 21 (56.8%) had primary refractory AML. At the time of HMA therapy, only one patient had favorable risk karyotype, whereas 69% and 23% had intermediate risk and poor risk karyotypes, respectively. Azacitidine and decitabine were used in 34% and 66% of patients, respectively. Patients had received a median of one line of therapy (range, 1-7) prior to HMA therapy. Of all patients who underwent HSCT, 23 (62%) had achieved a response (CR, CRi or hematologic improvement [HI]) to HMA therapy while the other 14 (38%) did not. Twenty-four patients (65%) went directly to HSCT after completing HMA therapy while 13 patients (35%) received additional therapy between HMA therapy and HSCT (**Table 2**). Of patients receiving no additional therapies between HMA and HSCT, a total of 16 patients had responded to HMA therapy (CR = 7, CRi = 8, HI = 1). Of patients who received some type of post-HMA therapy prior to HSCT, 7 patients had achieved a prior response to HMA (CR = 4, CRi = 2, HI = 1).

The median duration between last day of HMA therapy and HSCT was 50 days (range 6-210 days). Approximately 57% of patients received myeloablative conditioning therapy while the

other 43% received non-myeloablative conditioning regimens. Most patients received a matched unrelated donor transplant (56%) or a matched sibling transplant (24%), while 16% and 4% of patients received a haploidentical or a mismatched unrelated HSCT, respectively (**Table 2**).

Acute GvHD was observed in 40% of patients with 75% developing grade of 1 or 2 GvHD and 25% developing grade 3 or 4 GvHD. Acute GvHD affected skin (30%), mouth (10%), GI tract (45%) and liver (15%). Furthermore, 17% of patients developed chronic GvHD, which was limited in 75% and extensive in 25% of patients (**Table 2**). Chronic GvHD most commonly affected skin (40%), but also affected eyes and mouth (20%), GI tract (20%) and liver (20%). After HSCT, 7 patients (19%) received further lines of therapy with epigenetic therapy (HMA or histone deacetylase inhibitor therapy) (58%) being most commonly used while chemotherapy was rarely used (8%).

The median OS for the entire cohort of 37 patients, who underwent HSCT after HMA therapy was 15.3 months (95% CI 9.5 –21.7 months) from the start of HMA therapy. This was statistically significantly longer than the median OS for all other 618 patients, who did not receive a HSCT after HMA therapy (OS 6.4 months, 95% CI 5.7-6.9 months, $p < 0.0001$). The median OS was 14.6 months (95% CI 9.5 – not-reached) for patients with no therapies administered between HMA and HSCT and 15.3 months (95% CI 9.4 – not-reached) for patients with at least one therapy in between HMA and HSCT, respectively ($p = 0.3$) (**Figure 1A**).

For patients, who underwent subsequent HSCT without intervening therapies between HMA and HSCT, median OS was 16.8 months (95% CI 9.5 months - not reached) for the 16 patients

who achieved a response to HMA therapy (CR/CRi/HI) whereas it was 14.5 months (95% CI 6.7 months – not reached, p =0.4) for the 14 patients with either SD or PD (**Figure 1B**).

For patients without intervening therapies between HMA and HSCT, median OS was 29.7 months (95% CI 7.01 – not-reached) for patients who achieved a complete remission (CR) to HMA and 14.6 months (95% CI 9.47 – not-reached) for those not achieving CR (p = 0.6).

In summary, in one of the largest reported cohorts of patients with RR-AML treated with HMAs, we determined that a minority of patients underwent HSCT after completion of HMA therapy. While the median OS of the patients who underwent HSCT after HMA therapy was significantly longer compared to patients who did not undergo HSCT, only about 25% of the 24 patients who went to HSCT directly after HMA therapy were long term survivors (reached a plateau on the KM survival curve), which translates into just 6 patients out of the original 655 person cohort (<1%). Importantly, the OS for patients who achieved a CR with HMAs and went directly to HSCT was not statistically significantly different from patients who achieved a CR with HMAs but did not undergo HSCT (29.7 months vs. 25.3 months, p= 0.8). Furthermore, it did not seem to make a difference whether patients achieved a response to HMA therapy or not and whether patients went directly to HSCT after HMA therapy or had any other therapy after receiving HMA and prior to HSCT (**Figure 1**). These findings could argue against a benefit specific to HMA therapy when used as a bridge therapy to HSCT. While patients who achieved a CR with HMAs and thereafter underwent HSCT without intervening therapy, had a median OS reaching 30 months, this subgroup was too small to make any conclusions whether they had a

statistically significantly prolonged OS compared to patients who did not achieve a CR with HMA therapy.

Our study indicates that while HMAs can allow outpatient administration with lower toxicity compared to salvage intensive chemotherapy and can be used as a bridge to HSCT, only a minority of patients with RR-AML were able to undergo transplantation and the long survival rate was quite limited. As most patients do very poorly regardless of HMA response and regardless of receiving HSCT, improved treatments are urgently needed for patients with RR-AML. Combining HMAs with investigational therapies could lead to better outcomes in this difficult to treat patient population.

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Figure legends

Figure 1: Probability of overall survival from start of HMA therapy

A: For patients who directly went to HSCT vs. patients, who received at least one more line of therapy between HMA and HSCT

B: For patients, who directly went to HSCT stratified by having a response (CR,CRi,HI) vs. no response (SD, PD) to HMA therapy

Table 1: Patient characteristics of the 37 transplanted patients

Patient characteristics	N (% or Range)
Male/ Female	17/20 (46%/54%)
Age	56 (22-71)
Disease status	
Relapsed	16 (43.2%)
Primary treatment refractory	21 (56.8%)
Karyotype risk	
Favorable	1 (8%)
Intermediate	9 (69%)
Poor	3 (23%)
Azacitidine/ Decitabine	11/21 (34%/66%)
Response to HMA	23 (62%)
Complete remission (CR)	11 (30%)
Complete remission with incomplete count recovery (CRi)	10 (27%)
Hematological improvement (HI)	2 (5%)
No response to HMA	14 (38%)
Therapy between stop of HMA therapy and HSCT	
Yes/No	13/24 (35%/65%)
Type of therapy administered (18 therapies prescribed to 13 patients):	
CPX	5 (27.8%)
Cytarabine	5 (27.8%)
Clofarabine	3 (16.8%)
CLAG	2 (11.1%)
MEC	1 (5.6%)
FLAG Ida	1 (7.7%)
Cytoxan/Etoposide	1 (5.6%)
Therapy after HSCT	
Yes/No	7/30 (19%/81%)
Type of therapy administered (13 therapies prescribed to 7 patients):	
Azacitidine, Decitabine	6 (46.2%)
Cytarabine	2 (15.4%)
Hydroxyurea	2 (15.4%)
SGI-110	1 (7.7%)
ASP-2215	1 (7.7%)
Sorafenib	1 (7.7%)

Table 2: Transplant characteristics for patients, who underwent HSCT after HMA for RR-AML

	All patients (n = 37)	Patients with no subsequent therapies between HMA and HSCT (n = 24)	Patients with subsequent therapies between HMA and HSCT (n = 13)
Type of Graft (n = 25):			
Matched sibling	6 (24%)	4 (25%)	2 (22.2%)
Matched unrelated donor (MUD)	14 (56%)	9 (56.2%)	5 (55.6%)
Mismatched unrelated	1 (4%)	0 (0%)	1 (11.1%)
Haplotransplant	4 (16%)	3 (18.8%)	1 (11.1%)
Type of conditioning regimen (n = 14):			
Ablative	8 (57.1%)	7 (63.6%)	1 (33.3%)
Non-ablative	6 (42.9%)	4 (36.4%)	2 (66.7%)
Acute GVHD:			
Presence of acute GVHD (n=25)	10 (40%)	6 (40%)	4 (40%)
Severity/Grade of acute GVHD (n=8):			
Grade 1	3 (37.5%)	2 (50%)	1 (25%)
Grade 2	3 (37.5%)	1 (25%)	2 (50%)
Grade 3	1 (12.5%)	0 (0%)	1 (25%)
Grade 4	1 (12.5%)	1 (25%)	0 (0%)
Organ affected in acute GVHD (n = 20):			
Skin	6 (30%)	4 (33.3%)	2 (25%)
Eyes	2 (10%)	2 (16.7%)	0 (0%)
Gut	9 (45%)	5 (41.7%)	4 (50%)
Liver	3 (15%)	1 (8.3%)	2 (25%)
Chronic GVHD:			
Presence of chronic GVHD (n=24)	4 (16.7%)	3 (21.4%)	1 (10%)
Severity/Grade of chronic GVHD (n=4):			
Limited	3 (75%)	3 (100%)	0 (0%)
Extensive	1 (25%)	0 (0%)	1 (100%)
Organ affected in chronic GVHD (n=5):			
Skin	2 (40%)	2 (66.7%)	0 (0%)
Mouth	1 (20%)	1 (33.3%)	0 0%)
Gut	1 (20%)	0 (0%)	1 (50%)
Liver	1 (20%)	0 (0%)	1 (50%)